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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,230	02/25/2004	Tadamitsu Kishimoto	046124-5042-01	1453

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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/785,230	KISHIMOTO ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 25-30* is/are pending in the application.

4a) Of the above claim(s) *1-23,27,29 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 23, 2007 has been entered.

Claims 1-23 and 25-30 are pending. Claim 24 is canceled. Claims 1-23, 27, 29, and 30 remain withdrawn. Claims 25, 26, and 28 are amended. Claims 25, 26, and 28 are currently under prosecution.

Specification

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.8821 (a)(1) and (a)(2). Specifically, there are no SEQ ID NOs identified with the sequences disclosed on page 15, lines 13 and 19. MPEP 2421.02 states:

> The sequence rules embrace all unbranched nucleotide sequences with ten or more bases and all unbranched, non-D amino acid sequences with four or more amino acids, provided that there are at least 4 specifically defined nucleotides or amino acids. The rules apply to all sequences in a given application, whether claimed or not.

Applicant is required to provide (1) a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, (2) a substitutes paper copy of the "Sequence Listing", (3) an amendment directing the entry of that paper into the specification, and (4) a statement that the content of the paper and computer readable copies are the same, and, where applicable, include no new matter, as required by CFR 1.821(d) which requires a reference to a particular sequence identifier (i.e., SEQ ID NO:#) be made in the specification and claims wherever a reference is made to that sequence (See MPEP 2422.04).

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Inhibiting vascularization using antibodies to CXCR4 and SDF-1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 25, 26, and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a solid cancer

expressing human CXCR4, a method for treating a disease pathologically caused by neovascularization that expresses human CXCR4, and a method for suppressing vascularization in a subject expressing CXCR4 comprising administering an anti-human CXCR4 antibody or fragment thereof possessing binding activity to human CXCR4; or an anti-human SDF-1 antibody, or fragment thereof possessing binding activity to human SDF-1 wherein the antibodies inhibit binding between the human ligand SDF-1 and the human receptor CXCR4, does not reasonably provide enablement for a method for treating any solid cancer, a method for treating any disease pathologically caused by neovascularization, and a method for suppressing any vascularization in a subject regardless of human CXCR4 expression. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in

determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are broadly drawn to a method for treating any solid cancer, a method for treating any disease pathologically caused by neovascularization, and a method for suppressing any vascularization in a subject regardless of human CXCR4 expression, comprising administering an anti-human CXCR4 antibody or fragment thereof possessing binding activity to human CXCR4; or an anti-human SDF-1 antibody, or fragment thereof possessing binding activity to human SDF-1 wherein the antibodies inhibit binding between the human ligand SDF-1 and the human receptor CXCR4.

The specification discloses the amino acid sequence of human CXCR4 is known and is set forth in SEQ ID NO:1 (p. 14, lines 23-26). There are two types of SDF-1 differing in length of amino acid sequence: SDF-1α and SDF-1β. The amino acid sequence of human SDF-1α is set forth in SEQ ID NO:5 and the amino acid sequence of SDF-1β (SEQ ID NO:9) is derived from human SDF-1α by an addition of 4 amino acid residues to the C-terminus (p. 15, lines 5-14). The specification discloses that CXCR4 is expressed in developing vascular endothelial cells and that in knock-out mice lacking the ligand SDF-1 or its chemokine receptor, CXCR4, vascularization in the mice is suppressed. The specification contemplates inhibiting SDF-1 or CXCR4 with antibodies to treat disease involving neovascularization including development of solid

tumors (p. 2, line 20 – p. 5, line 22; p. 17, lines 13-p. 18, line 16; p. 38, lines 15-26; Examples).

The art teaches that anti-human CXCR4 antibodies or anti-human SDF-1 antibodies inhibit tumor growth or tumor cell proliferation, wherein the tumor cells express human CXCR4 or its ligand human SDF-1. Bertolini et al (Cancer Research, 2002, 62:3106-3112) teach that SDF-1 (also known as CXCL12) and its monogamous receptor CXCR4 are involved in trafficking of B cells and hematopoietic progenitors (abstract). Bertolini et al teach a tumor challenge trial wherein antibodies to human CXCR4 treated mice with non-Hodgkin's Lymphoma tumors. Tumor growth was abrogated in the majority of mice treated and was significantly delayed in the remaining group (abstract; Figs 5 and 6). Bertolini et al also teach administering antibodies that bind human SDF-1 or CXCR4 *in vitro* to AML cells wherein each of the antibodies reduced the proliferation of AML cell lines and the survival of primary AML cells. Bertolini et al suggests that survival and proliferation of AML cells are mediated by SDF-1/CXCR4 interactions and autocrine secretion of SDF-1 (p. 2818, col. 2; Fig. 4; p. 2819, col. 2 through p. 2820, col. 1). US Patent 6,863,887, Murphy et al (filed March 29, 1999, issued March 8, 2005) teach methods of inhibiting the proliferation of tumor cells that over-express human CXCR4 comprising administering an antibody specific for human CXCR4 (see claims 1-19).

The art teaches the treatment of conditions caused by neovascularization using antibodies that bind to human CXCR4 or SDF-1. For example, Butler et al (J of Clinical Investigation, 2005, 115:86-93) teach that intravitreal injection of antibodies that bind

human SDF-1 prevented retinal neovascularization in a murine model (abstract; Figure 6). Butler et al suggest that blocking SDF-1 function can prevent neovascularization and may serve as an important advancement in the treatment of ocular disease such as diabetic retinopathy, and that the intravitreal injection of a blocking antibody to SDF-1 can work to block neovascularization in their acute injury model for up to one month (p. 87, col. 1). Butler et al suggests that SDF-1 may be a key player in angiogenesis and in the progression of proliferative retinopathy and that antibodies that block SDF-1 activity may provide a safe and effective alternative treatment for ischemic diseases such as proliferative diabetic retinopathy and diabetic macular edema (p. 91, col. 2). Sengupta et al (Investigative Ophthalmology & Visual Science, 2005, 46:343-348) teach that injection of mice subretinally with antibodies to SDF-1 significantly reduced the size of choroidal neovascularization (CNV) lesions in the eyes (abstract). Walter et al (Circulation Research, 2005, 97:1142-1151) teach that transplantation of bone marrow cells as well as circulating endothelial progenitor cells (EPC) enhances neovascularization after ischemia and that the chemokine receptor is essential for migration and homing of hematopoeitic cells. Walter et al teach that incubation of endothelial progenitor cells (EPC) from healthy volunteers with neutralizing antibodies to CXCR4 profoundly inhibited vascular endothelial growth factor- and SDSF-1-induced migration as well as EPC-induced angiogenesis in an *ex vivo* assay (abstract). Preincubation of transplanted EPC with CXCR4 antibody reduced EPC incorporation and impaired blood-flow recovery in ischemic hind limbs of nude mice (abstract). Walter et al conclude that CXCR4 receptor signaling profoundly modulates the angiogenic

activity and homing capacity of cultured EPC (abstract). Finally, Tachibana et al (Nature, 1998, 393:591-594) teach that SDF-1 and CXCR4 define a new signaling system for organ vascularization and demonstrate that mice lacking CXCR4 or SDF-1 have defective formation of large vessels supplying the gastrointestinal tract. Further, mice lacking CXCR4 die *in utero* and are defective in vascular development, haematopoiesis and cardiogenesis, like mice lacking SDF-1, indicating that CXCR4 is a primary physiological receptor for SDF-1 (abstract).

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide guidance or examples for treating a solid cancer, treating a disease pathologically caused by neovascularization, or suppressing vascularization comprising administering an anti-human CXCR4 antibody or anti-human SDF-1 antibody wherein the solid cancer, disease or vascularization condition do not express human CXCR4, the receptor for human SDF-1 ligand. The art teaches that while many different solid tumors express CXCR4 and SDF-1, not all tumors express CXCR4 or SDF-1 (CXCL12). Jiang et al (Gynecologic Oncology, 2006, 103:226-233) teach that SDF-1 was detected in 91% and CXCR4 was detected in 59% of patients with primary epithelial ovarian tumors (abstract). Marini et al (J of Clinical Oncology, 2007, ASCO Annual Meeting Proceedings Part I, Vol 25, No. 18S, 2007: abstract# 21159) teach that CXCR4 was expressed in only 20% of breast cancer patients (see entire abstract). Given the teaching of the art, one of skill in the art could not predictably practice the claimed invention unless the cancer, disease pathologically caused by neovascularization, or vascularization condition expresses chemokine

receptor CXCR4. The art recognizes the requirements for successful immunotargeting in cancer protocols as disclosed by White et al. (Ann. Rev. Med., 2001, 52:125-145). In particular, White teaches that, for successful targeting and immunotherapy, besides specificity of the antibody for the antigen, other properties of the antigen should be considered including that the antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating (p. 126, second paragraph). Given the teaching of the art, one of skill in the art could not predictably practice the claimed invention and a high quantity of experimentation would be required unless the cancer, disease pathologically caused by neovascularization, or vascularization condition all express human chemokine receptor CXCR4, whose activation would be blocked by the claimed antibodies.

Therefore, in view of the state of the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

5. All other rejections recited in the Office Action mailed February 27, 2007 are hereby withdrawn.

6. **Conclusion:** No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura B Goddard, Ph.D.
Examiner
Art Unit 1642